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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,598	11/03/2005	Pierrette Gaudreau	AKL-001	7604

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
12/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/527,598	GAUDREAU, PIERRETTE	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48 and 81-97* is/are pending in the application.

4a) Of the above claim(s) *94,96 and 97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,81-93 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/12/2009 has been entered.

Election/Restrictions

2. Claims 48 and 81-97 are pending. Applicant's election of the species pharmaceutical composition in a formulation suitable for injection **without** traverse in the reply filed on 02/17/2009 is acknowledged. Prior art was found on this species which reads on claim 91 and additionally on topical, inhalation and oral administration which read on claims 92, 93 and 95, respectively. In accordance with MPEP § 803.02 the search was not extended. Claims 94, 96 and 97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Information Disclosure Statement

3. The information disclosure statements filed 11/12/2009 has been considered.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 48 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaudreau (U.S. Patent No. 5,854,216, cited reference A1 on the Information Disclosure Statement filed 2/7/2007).

6. Claim 48 is drawn to a pharmaceutical composition comprising a GHRH analogue consisting of Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser- D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2 and a pharmaceutically acceptable carrier. The only structural requirements for the claimed composition are the structure of the GHRH analogue and the presence of the pharmaceutically acceptable carrier. The claim also states that the GHRH analogue is present in an amount effective to stimulate secretion or synthesis of growth hormone in a human in need thereof. This phrase constitutes an intended use for the claimed composition. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

7. Gaudreau teaches a GHRH analogue consisting of:

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser- D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

(Tables 10 and 11, compound 8). This analogue is identical to the analogue recited in instant claim 48. Gaudreau teaches that this peptide was synthesized using solid-phase methods (final solvents and conditions were not reported) and added in increasing concentrations (0 to 1000 nM) to anterior pituitary homogenates in 300 µl of Tris-HCl buffer, pH 7.4, containing 5 mM EDTA, 5mM MgCl2 and 0.42% BSA (col 12, lines 51-67). Gaudreau teach that this GHRH

analogue exhibits a binding affinity to the receptor in rat adenopituitary cells equivalent to that of wild type hGRF(1-29)NH_2 (Table 11).

8. Gaudreau does not explicitly teach that this GHRH analogue was formulated with a pharmaceutically acceptable carrier.

9. It would have been obvious to make this GHRH analogue and to dissolve it in a pharmaceutically-acceptable carrier at a concentration effective to stimulate secretion or synthesis of growth hormone in rat. The skilled artisan would have been motivated to do so based on the teaching of Gaudreau that this GHRH analogue exhibits a binding affinity to the receptor in rat adenopituitary cells equivalent to that of wild type hGRF(1-29)NH_2 (Table 11), a property which warrants further study on the ability of the compound to activate the receptor *in vivo* and to stimulate growth hormone secretion and synthesis. A better understanding of the *in vivo* activity of GHRH analogues, such as compound 8 taught by Gaudreau, is critical for formulating a structure-activity relationship for these compounds which can be applied to the development of therapeutic GHRH analogous. This line of study would be motivated by Gaudreau's teaching that related peptides can be used to treat a variety of conditions such as hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union-bone fracture, wounds, post-surgical problems, lactation failure, female infertility, cachexia, T-cell immunodeficiencies, neurodegenerative conditions and GRF receptor-dependent tumors (claim 3). Because compound 8 exhibits binding to the rat receptor *in vitro*, the skilled artisan could use compound 8 to determine if the particular structure of compound 8 permits binding to the receptor and activation, or binding without activation, and in doing so gain a better understanding of the molecular contribution that the residues that have been mutated in this

analogue relative to the wild-type sequence contribute to function. In order to administer compound 8 to a rat, the skilled artisan would have been motivated to combine the peptide with a pharmaceutically acceptable carrier suitable for various modes of administration including injection and topical. There would have been a reasonable expectation of success given that the GHRH analogue peptides can be synthesized using solid state methods, and formulated in pharmaceutically acceptable carriers, and that the GNRH analogue possesses biological activity.

10. The resulting composition would meet all of the structural limitations of the instant claims. There is no structural difference between the claimed invention and the composition that is obvious over the prior art of Gaudreau, and as a result, the instant claims are not patentably distinguished from the prior art. A pharmaceutically acceptable carrier for rats is not structurally different from a pharmaceutically acceptable carrier for humans. As a result, the GHRH analogue taught by Gaudreau formulated for administration to and testing in rats would be capable of being administered to humans, meeting the functional and intended use limitations of claim 48.

11. In the response filed 11/12/2009 and in the declaration filed by Dr. Gaudreau under 37 CFR § 1.132, Applicant traverses the rejection on the grounds that Applicant has obtained unexpected and surprising results with respect to the species recited in instant claim 48. On. p. 7 of the response Applicant states:

> Applicant has found, unexpectedly, that the binding affinity of the claimed GHRH analogue to the receptor in rat adenopituitary cells is not indicative of the binding affinity for the human GHRH receptor. Applicant notes that the difference between the binding affinity in the rat adenopituitary cells and the human GHRH receptor (hGHRH-R) in baby hamster kidney (BHK) cells transfected with hGHRH-R was discovered during the course of Applicant's subsequent investigation.

Applicant argues that prior to this discovery the standard for investigation in the field was to perform the *in vitro* assay with the rat receptor and to select candidates with high activity in the *in vitro* assay for further testing. Based on this standard practice, Applicant argues that the skilled artisan a) would never have tested the instantly claimed compound, and b) that its superior activity is entirely unexpected. On p. 8 of the response filed 11/12/2009 (see also the declaration filed by Dr. Gaudreau under 37 CFR 1.132) Applicant writes:

> In the field of research for GHRH analogues, it is well accepted that an *in vitro* rat pituitary cell assay is used as a screen to select the most active GHRH analogues for further testing. (See Gaudreau Declaration, paragraph 3). In support of this assertion, Dr. Gaudreau cites numerous papers that show that an *in vitro* rat pituitary cell assay was considered a standard test for testing of GHRH analogues prior to undergoing in vivo testing. (See Gaudreau Declaration, paragraphs 3-14). In the papers cited compounds showing an enhanced relative potency and binding affinity compared to a standard during in vitro testing using a rat pituitary cell assay were selected for *in vivo* testing. (See Gaudreau Declaration, paragraphs 3-14). In the papers cited, none of the compounds having a relative *in vitro* potency, in the rat pituitary cell assay, that was less than or equal to that of the standard were selected for *in vivo* testing. (See Gaudreau Declaration, paragraphs 3-14)

Applicant argues that Dr. Gaudreau's decision to test the instantly claimed analogue that exhibited a nearly equal binding affinity to natural hGHRH in the *in vitro* assay was "a break from precedent" (p. 9), a claim that is supported by the citation of numerous prior art documents. Applicant reports that the *in vitro* potency index of the instantly claimed compound is the highest of the analogues tested (specification paragraph 0090) and argues that this property was not taught or suggested by the cited references and that on the contrary, the cited references "would lead one of ordinary skill in the art to believe that the claimed... analogue would <u>not</u> bind to human GHRH any better "than the wild type hGHRH(1-29)-NH_2."

12. This argument has been fully considered but is not persuasive.

13. First, with respect to motivation to choose the claimed analogue from amongst the analogues taught by Gaudreau, although the practice in the prior art of developing drugs for human is to select the analogues that perform better in the *in vitro* rat receptor binding assay than the wild-type human GHRH, other reasons exist for selecting compound 8, an analogue that performs equal to the wild-type human GHRH. For example, compound 8 of Gaudreau could be used to stimulate growth hormone secretion or synthesis in rat. The fact that the data presented by Gaudreau suggests that compound 8 binds to the rat receptor suggests that it will stimulate growth hormone secretion or synthesis in rat. If not, compound 8 would represent an analogue with an ability to bind to its target receptor but not activate it, which could form the basis for a structure-activity study of the GHRH sequence. In response to Applicant's argument that compound 8 has superior activity to the other analogues tested, the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In the instant case, it would have been obvious to make a pharmaceutical composition comprising compound 8 and a pharmaceutically acceptable carrier in order to test its *in vivo* activity in rats for the purpose of conducting structure-activity studies on GHRH. The superior *in vitro* potency of this composition flows naturally from the composition that is obvious over Gaudreau.

14. Second, with respect to Applicant's allegation of unexpected results, MPEP § 2144.09. VII. states: "However, a claimed compound may be obvious because it was suggested by, or structurally similar to, a prior art compound even though a particular benefit of the claimed compound asserted by patentee is not expressly disclosed in the prior art. It is the differences in

fact in their respective properties which are determinative of nonobviousness. If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compound from the prior art. *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)." In the instant case, the prior art analogue is identical to the analogue recited in claim 48. Therefore, although the prior art does not teach that this analogue has a superior *in vitro* potency, the analogue must in fact possess this property, rendering the claimed composition obvious. The difference between the claimed composition and the composition taught by Gaudreau is the presence of a pharmaceutically-acceptable carrier. Given that the analogue structure, not the carrier, is critical for the functional properties of the claimed composition, this difference is not determinative of nonobviousness.

15. Finally, with respect to Applicant's allegation of unexpected results, MPEP § 716.02(d) states: "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)" In the instant case, the scope of the claim is not limited a composition that is administered to humans. Although the claim recites an intended use for the composition, based on its structure and components, the claimed composition could also be administered to other mammals and to a variety of patient populations in need of growth hormone stimulation. Applicant's unexpected results pertain only to humans which is not commensurate with the full breadth of the claims.

16. For these reasons, the rejection is maintained.

17. Claims 81-91, 93 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaudreau (U.S. Patent No. 5,854,216, cited reference A1 on the Information Disclosure Statement filed 2/7/2007), as applied to claims 48 and 92 above, in further view of Seely et al. (U.S. Patent No. 5,137,872).

18. Gaudreau does not teach a pharmaceutical composition comprising sterile water, saline, buffered solution, diluents, stabilizers, preservatives, wetting agents, emulsifying agents, pH buffering agents, or viscosity enhancing agents or pharmaceutical compositions suitable for injection

19. Seely et al. teach a method for stimulating the release of GH in animals comprising administering to the animals an amount of the hGRF analogs sufficient to stimulate the release of GH. Seely e al. teach means of formulating the GRF analogues for administration.

20. It would have been obvious to formulate the GHRH analogues of Gaudreau according to the teaching of Seely et al. With respect to claim 81, Seely et al. teach combining the hGRF analogues with sterile aqueous solution (col 9, line 6). With respect to claim 82, Seely et al. teach the use of saline as a pharmaceutically acceptable carrier (col 11, lines 49-50). With respect to claim 83, Seely et al. teach the use of a buffered solution as a pharmaceutically acceptable carrier (col 11, lines 49-50, col 9, line 23). With respect to claim 84, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a

diluent (col 8, line 44). With respect to claim 85, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a stabilizer (additives which enhance the stability, col 9, line 21). With respect to claim 86, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a preservative (col 9, line 22). With respect to claims 87, 88 and 90, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a wetting agent, an emulsifying agent or a viscosity-enhancing agent such as ethanol, polyol (for example glycerol, propylene glycol, liquid polyethylene glycol), vegetable oils (for example, cottonseed oil, sesame oil, olive oil, soybean oil, corn oil, sunflower oil, or peanut oil), isopropyl myristate, parabens, chlorobutanol, phenol, sorbic acid, aluminum monostearate and gelatin (col 9, lines 4-35). With respect to claim 89, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a pH buffering agent (col 11, lines 49-50, col 9, line 23). With respect to claims 91, 93-95, Seely et al. teach that hGRF analogues may be administered nasally, orally or by injection such as by intravenous, intramuscular, subcutaneous, or intraperitoneal injection, or by subcutaneous implant (col 8, line 61 - col 9, line 3). The formulations taught by Seely et al. represent obvious variants of pharmaceutical formulations for GNRH analogues.

21. In the response filed 11/12/2009 traversed the rejection on the same reasons cited in the rejection of claims 48 and 92 over Gaudreau which were addressed above. Therefore, for the same reasons, this rejection is maintained.

Double Patenting - Withdrawn

22. The rejection of claims 48, 81-91, 93 and 95 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 12/171,447 is withdrawn in view of the terminal disclaimer filed 11/12/2009.

Conclusion

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:30 P.M.

25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb